



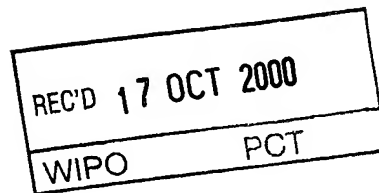
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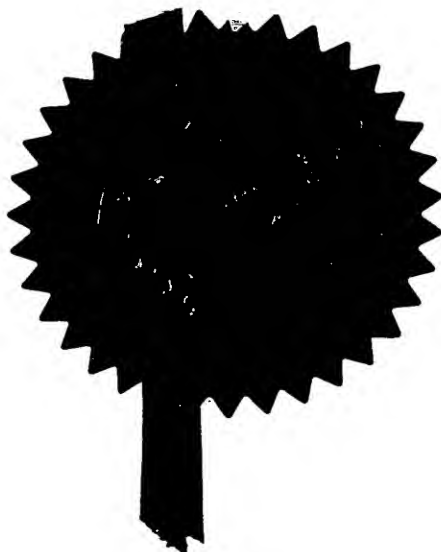


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LT99 E482541-1 D00032  
F01/7700 0.00 - 9923738.0

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The Patent Office

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1. Your reference JIM/LJ/P13885

2. Patent application number  
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**9923738.0**

**- 7 OCT 1999**

3. Full name, address and postcode of the or of each applicant (underline all surnames)

SOCIÉTÉ DES PRODUITS NESTLÉ SA  
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CH-1800 VEVEY  
SWITZERLAND

Patents ADP number (if you know it)

730762002

If the applicant is a corporate body, give the country/state of its incorporation

SWITZERLAND

4. Title of the invention

NUTRITIONAL COMPOSITION

5. Name of your agent (if you have one)

ELKINGTON AND FIFE

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

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Patents ADP number (if you know it)

67004

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and (if you know it) the or each application number

Country

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Number of earlier application

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# Patents Form 1/77

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YES

- a) any applicant named in part 3 is not an inventor, or
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I/We request the grant of a patent on the basis of this application.

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Date

07/10/1999

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Mr J I MARCHANT  
01732 458881

## Nutritional Composition

The present invention relates to a nutritional or therapeutic composition for oral administration which comprises a naturally occurring precursor that is metabolised to a compound having anandamide activity for use as a medicament or nutritional product, a method of production of the composition, use of the composition in the manufacture of a nutritional or therapeutic composition for the treatment or prevention of a behavioural disorder; and a method of treatment or prevention of a behavioural disorder which comprises administering an effective amount of the composition.

Within the context of this specification the word "comprises" is taken to mean "includes, among other things". It is not intended to be construed as "consists of only".

Standard nomenclature for fatty acid compounds is used. For example, the number of carbon atoms and number and position of double bonds is typified by "20:4(5,8,11,14)" for arachidonic acid: the number preceding the colon is the total number of carbon atoms, the number immediately following the colon is the number of double bonds, and the numbers in parentheses are the position of the double bonds, starting from the end of the chain bearing the carboxylic acid group. In all compounds referred to in this manner, except where otherwise indicated, all double bonds are cis.

Standard nomenclature for classes of fatty acid compounds is used indicating the location of the double bond closest to the methyl end group, typified by "n-3" or "n-6": the number following the dash denotes the position of the double bond closest to the methyl end of the molecule, counting from the methyl end. Thus, arachidonic acid is in the n-6 class, as is linoleic acid (18:2(9,12)), whereas eicosapentaenoic acid (20:5(5,8,11,14,17)) is in the n-3 class. This nomenclature is equivalent to "omega or  $\omega$ " nomenclature in the literature, " $\omega$ " and "n" being interchangeable.

Anandamide (also referred to as *N*-arachidonyl ethanolamine) is an example of an *N*-acyl ethanolamine (hereinafter referred to as NAE). Both NAEs and *N*-acyl amines (hereinafter referred to as NAAs), an example of the latter of which is oleamide, are naturally occurring in the human body. They have been found in the hippocampus, striatum, cerebellum, spleen, heart, plasma and cerebral spinal fluid as well as in human milk.

The term "anandamide activity" is used within the context of this specification to mean an activity selected from the group which comprises an activity attributed

to the drug 9-tetrahydrocannabinol (THC), as well as affects specific to anandamide and 1- and 2-monoarachidonylglycerol isomers (hereafter denoted AG), and unique from THC. It has been suggested that anandamide and AG activities are typically, but not necessarily, mediated by binding to the receptor class, known as CB1 and CB2 receptors. These anandamide activities include, but are not limited to: antinociception, catalepsy and inhibition of locomotor activity *in vivo* and displacement of 9-tetrahydrocannabinol (THC), inhibition of adenylate cyclase, inhibition of calcium channels, activation of phospholipase A<sub>2</sub>, release of intracellular calcium *in vitro* and inhibition of twitch response *ex vivo*.

The term anandamide, as used within the context of this specification, refers to an NAE, NAA or MAG having anandamide activity (as defined above). Accepted scientific nomenclature will be used in this specification when reference is made to specific acyl moieties of an NAE, NAA or MAG.

It is well known that pharmaceutical compounds have wide application for their calming effects and they may be used in the treatment of patients suffering from conditions such as hypertension, glaucoma, insomnia, pain, inflammation, migraine headaches, convulsions, loss of appetite, nausea, cramps, diarrhoea, asthma, nervousness, aggressive behaviour, excessive timidity, inability to sleep, catalepsy, low mood, depression, gut upsets, or spasms, poor motor control, tics, excessive stress, spasticity or multiple sclerosis. However, a number of these compounds are not naturally occurring in nature and in view of this, patients may be reluctant to be administered them. In the light of this there is a need for the provision of new products which include naturally occurring precursors of compounds that have a nutritive or therapeutic effect, when metabolised endogenously to active compounds with anandamide activity.

Furthermore, a problem with most commercially available drugs is that they give rise to side effects such as nausea, bloating, cramping, etc. Clearly there is a need for a composition which does not give rise to these side effects.

The method of administration of a nutritive or therapeutic compound is an important consideration. Intravenous or subcutaneous administration of drugs requires expertise, and compared to oral administration it is not as safe, convenient or acceptable to the patient. In the light of these concerns it is clear that there is a need for new nutritive or therapeutic products which may be administered orally.

In addition to the problems set out above, infant formulae are generally constructed so that they resemble human milk as closely as possible, however a plurality of components in human milk are bioactive and, because of synergies among the components, the inclusion of only one or a few of them may not

reproduce the bioactivity of human milk. In view of this, a problem which presently faces researchers lies in the formulation of infant formulae or weaning foods which have components that are present in human milk and which have an equivalent activity to human milk. The problem is compounded in view of the fact that not all of the components in human milk have been identified and there are variations in the concentration of components which are present, possibly due to variations of mother's diets.

A further problem which faces nutritionists lies in the field of pet nutrition. Whereas some pets are aggressive, others are excessively timid. Muzzles have been provided which fit over the heads of aggressive animals and cover their mouths. This may not be a good solution in view of the fact that a muzzle may serve to aggravate the animal. In the light of this, there is a need for alternative solutions for calming excessively aggressive or timid pets.

US 5874459 discloses that anandamide may act as a ligand which interacts with cannabinoid receptors in the central nervous system and gut (CB1 receptors) and/or immune cells and tissues such as spleen, thymus and lymphocytes (CB2 receptors). Furthermore, this document indicates that interactions between anandamide and these two types of cannabinoid receptors have been shown to induce physiological effects. It is described that non-arachidonyl NAEs and NAAs have been shown to inhibit anandamide inactivating enzyme. This inhibition has the net effect of potentiating the effect of anandamide.

It has been suggested that a family of NAEs and NAAs as well as *sn*-1 and *sn*-2 monoarachidonyl glycerides are agonists of anandamide receptors (here anandamide receptor refers to a receptor that anandamide might bind to, including CB1, CB2, non-CB receptors) and elicit responses analogous to that elicited by anandamide. The chemical structures of NAEs and NAAs are based on fatty acids and depending on the specific fatty acids esterified they have been shown to have different activities. For example, whereas anandamide interacts with both the CB1 receptor of the central nervous system and the CB2 receptor of the immune system, palmitolyethanolamide may interact with the CB2 receptor but not the CB1 receptor and has an anti-inflammatory effect but no known neural effect.

Nature, vol 396, page 636, (1998) discloses the results of an analysis wherein NAEs and 2 arachidonoylglycerol (2-AG) were identified from foods including human, bovine and goat milk and cocoa at various stages of processing. The document suggests that anandamide (300mg/kg body weight<sup>-1</sup>) and 2-arachidonoylglycerol (400mg/kg body weight<sup>-1</sup>) have bioactivity when taken orally in mice, however the compounds were active only at very high concentrations relative to the concentrations normally present in foods and the results obtained show that

the amounts of anandamide, 2-AG and oleamide in foods, including milk and cocoa, are several orders of magnitude below those required if administered by mouth, to reach the blood and cause observable "central effects". However, the document indicates that pure doses of anandamide, 2-AG and oleamide have  
5 calming effects and effects on the immune system when *injected* into animals. Calming effects are characterised by lessened activity, decreased nociception and greater propensity for sleep.

US 568955 discloses that synthetically produced polyunsaturated fatty acid  
10 amides and their derivatives are able to mimic the effect of naturally occurring anandamides in the brain and bind to the cannabinoid receptor. The compounds described exhibit physiological activity and are reported as being useful active ingredients in pharmaceutical compositions for treatment of inflammation, migraines, spasticity, glaucoma and multiple sclerosis.

Remarkably it has now been found that a composition for oral administration may be provided which includes a precursor that is metabolised endogenously to form a compound having anandamide activity. It is particularly surprising that a dietary precursor is selectively taken up by the CNS and selectively incorporated  
20 into the NAE pool to serve as a CB receptor-binding ligand. In addition, it is remarkable that a dietary precursor induces only a small change in the phospholipid acyl composition but induces a large change in the NAE composition.

25 The invention addresses the problems set out above.

Accordingly, in a first aspect the invention provides a nutritional or therapeutic composition for oral administration which comprises a naturally occurring precursor that is metabolised to a compound having anandamide activity for use  
30 as a medicament or nutritive product.

In a second aspect the invention provides a method of production of a nutritional or therapeutic composition for oral administration which comprises the steps of identifying, purifying or synthesising a naturally occurring precursor that is  
35 metabolised to a compound having anandamide activity.

In a third aspect the invention provides use of a precursor which is metabolised to a compound having anandamide activity in the manufacture of a nutritional or therapeutic composition for the treatment or prevention of an anandamide-mediated ailment selected from the group which comprises hypertension,  
40 glaucoma, insomnia, pain, inflammation, migraine headaches, loss of appetite, nausea, cramps, diarrhoea, gut upsets, intestinal motility disturbances, asthma, nervousness, aggressive behaviour, excessive timidity, inability to sleep,



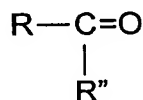
catalepsy, low mood, depression, spasms, poor motor control, tics, excessive stress, spasticity, multiple sclerosis and vocalization, poor language acquisition, skin inflammation and excess nociception.

5 Vocalization is taken to mean disturbances in vocalisation and vocalization related to bonding behaviour, for example between an infant and mother. Such vocalisations are important in animal husbandry and in successful nurturing of the offspring by the mother in household pets. Further, such behaviours as chronic sustained crying in human infants may be treatable by oral administration  
10 of an embodiment of a composition according to the invention.

Oral administration of an embodiment of a composition according to the invention may also be used to treat or prevent inflammation in superficial  
15 mammal-tissues (e.g., skin) by modulating levels of compounds with anandamide-like activity in these tissues.

In a forth aspect the invention provides a method of treatment of an anandamide-mediated ailment selected from the group which comprises hypertension, glaucoma, insomnia, pain, inflammation, migraine headaches, loss of appetite,  
20 nausea, cramps, diarrhoea, gut upsets, intestinal motility disturbances, asthma, nervousness, aggressive behaviour, excessive timidity, inability to sleep, catalepsy, low mood, depression, spasms, poor motor control, tics, excessive stress, spasticity, multiple sclerosis and vocalization, poor language acquisition, skin inflammation and excess nociception which comprises administering an  
25 effective amount of an embodiment of the composition according to the invention.

Preferably the precursor that is metabolised to a compound having anandamide activity comprises a long chain polyunsaturated fatty acid (LCPUFA) or  
30 derivative thereof. More preferably it comprises a compound of the general formula X:



Wherein R is the alkenyl moiety of a LCPUFA of total chain length 16-28 carbon atoms with 2-6 double bonds, with the first double bond at the c-1, c-3 c6, c7, c9 c12 position, counting from the non carboxyl (methyl) part of the molecule; and  
35 where R'' is selected from -H, lower alkyl, -OH, NH<sub>3</sub>, and NHCH<sub>2</sub>CH<sub>2</sub>OH, or an acid addition salt or complex thereof.

More preferably the precursor comprises a plurality of the formula X. Preferably 1-3 X molecules are esterified to a glycerol backbone, in the following stereochemical configurations: *sn*-1,2,3; *sn*-1,2; *sn*-1,3; *sn*-2,3; *sn*-1; *sn*-2; *sn*-3.

5 In an alternative embodiment the LCPUEA is a polyunsaturated fatty acid of 16-28 carbon atoms with 2-6 double bonds, having methylated-, branched-, cyclic-, conjugated-, non-methylene interrupted-, epoxy-, furanoid-, hydroxyl-, allylic-, trans-, and seleno- moieties.

10 More preferably the fatty acid is selected from the group which comprises arachidonate (20:4n-6 AA), linoleate (18:3n-6), gamma linolenate (18:3n-6), dihomogammalinolenate (20:3n-6 DGLA), adrenic acid (22:4n-6), linolenate (18:3n-3), stearidonic (18:4n-3), eicosatetraenoic (20:4n-3), eicosapentaenoate (20:5n-3), docosahexaenoate (22:6n-3DHA), docosapentaenoate (22:5n-3 or  
15 22:5n-6), tetracosapentaenoate (24:5n-3 or 24:5n-6), tetracosahexaenoate (24:6n-3) or the Mead acid (20:3n-9).

Preferably, an embodiment of a composition according to the invention includes an inhibitor of anandamide-inactivating enzyme (also known as amidase).  
20 Preferably the inhibitor is selected from the group which comprises oleate and oleamide, palmitate, palmitoylethanolamide, linoleylethanolamide, 2 palmitoylglycerol, 2-linoleylglycerol.

25 Preferably an embodiment of a composition according to the invention comprises a mixture of a saturated molecule in combination with an unsaturated precursor that is metabolised to a compound having anandamide activity. Preferably, the saturated molecule is palmitate or palmitoylethanolamide. Preferably the unsaturated precursor is arachidonic acid. This provides the advantage that the anandamide activity of the metabolite formed endogenously is potentiated by  
30 both inhibiting the breakdown of a metabolite having anandamide-like activity and by the saturated NAE compound binding to the CB2 receptor.

35 Preferably, an embodiment of a composition according to the invention comprises a mixture of a compound which reacts with a CB receptor in combination with a precursor that is metabolised to a compound having anandamide activity and an inhibitor of the amidase. This provides the advantage of synergy between the active molecules and potentiation of their effect by inhibiting the breakdown of a metabolite having anandamide-like activity.

40 Preferably, the precursor that is metabolised to a compound having anandamide activity is a free fatty acid, fatty acid ester of an alcohol, or a triacylglycerol. More preferably it is a triacylglycerol having an active fatty acid at the *sn*-1 and

*sn*-2 position. This provides the advantage that it leads to particularly effective CB receptor agonism. Most preferably, the triacylglycerol comprises both the active precursor compounds (eg arachidonate) and the potentiator compounds (eg palmitate). This provides the advantage of a particularly effective mixture.

5 Preferably, an embodiment of a composition according to the invention comprises a structured triacylglycerol prepared by the interesterification of triacylglycerols with active fatty acids so that a bioactive fatty acid is found in the *sn*-2 position of the triacylglycerol. This provides the advantage of  
10 optimising delivery of the active FA to body tissues, particularly the brain.

Preferably an embodiment of a composition according to the invention comprises a physiologically acceptable carrier diluent or adjuvant.

15 Preferably an embodiment of a composition according to the invention comprises a combination of a naturally occurring precursor that is metabolised to a compound having anandamide activity together with a typical steroidal or non-steroidal anti-inflammatory drug (NSAID). This provides the advantage that synergy occurs since the combination has the ability to diminish inflammation  
20 via different pathways.

Preferably, an embodiment of a composition according to the invention comprises a precursor of a CB1 receptor agonist (eg anandamide) in combination with a precursor of a CB2 receptor agonist (eg Palmitoylethanolamide). This  
25 provides the advantage that the anti-pain effect of the metabolites is about 100 times stronger than the effect provided by the metabolites of either precursor individually.

Embodiments of the invention will now be described in further detail with  
30 reference to the accompanying drawings in which:

Figure 1 shows the chemical structure of *N*-arachidonyl ethanolamine (anandamide), 2-AG, and oleamide.

35 Figure 2 shows the effects of oral cannabimimetic lipids on ambulation, rearing, immobility and analgesia.

Figure 3 shows the effects of oral administration of olive oil, anandamide, 2-AG, THC and oleamide on ambulation, rearing, immobility and analgesia.

40 Ambulation, rearing, and immobility parameters were statistically, significantly different between the treatment groups and the control group,  $p < 0.01-0.05$ , ANOVA, Newman-Keuls; Only THC statistically, significantly increased analgesia.

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	18:2n-6 ~ 18:3n-3 deficient			18:2n-6 ~ 18:3n-3 adequate			
Fatty Acid	No LCP	Egg+ fish Oil	Single cell oil	No LCP	Egg + fish oil	single cell oil	Sow milk
	g/100g fatty acids						

8:0	8.0	7.0	7.4	17.2	15.5	14.9	
10:0	6.7	5.9	6.5	13.5	12.6	13.0	
12:0	44.2	39.7	42.9	1.0	0.3	0.3	0.1
14:0	17.1	15.6	16.8	0.8	0.6	0.6	2.4
16:0	9.5	10.5	9.5	11.3	12.1	10.9	28.1
18:0	3.4	4.0	3.5	3.2	3.5	3.3	5.6
16:1	0.1	0.34	0.1	0.1	0.3	0.2	4.7
18:1	8.1	10.4	9.3	33.3	33.4	35.1	32.6
18:2n-6	1.6	3.8	1.9	15.6	16.0	16.4	20.4
18:3n-6	-	0.6	0.1	-	0.4	0.1	0.2
20:2n-6	-	-	-	-	-	-	0.4
20:3n-6	-	-	-	-	-	-	0.2
20:4n-6	-	0.1	0.4	-	0.1	0.4	0.7
22:4n-6	-	-	-	-	-	-	0.1
18:3n-3	0.1	0.5	0.1	1.5	1.8	1.6	2.3
20:5n-3	-	0.1	-	-	0.1	-	0.1
22:5n-3	-	-	-	-	-	-	0.6
22:6n-3	-	0.3	0.3	-	0.3	0.3	0.1

Changes in individual brain phospholipid classes that occurred after feeding were analysed.

5 The results showed that the addition of 20:4n-6 and 22:6n-3 to diets containing adequate levels of essential fatty acids (18:2n-6 and 18:3n-3) lead to an increase in 22:6n-3 in phosphatidyl choline; a decrease in 22:5n-6 in phosphatidyl ethanolamine; and no change in arachidonate (20:4n-6) in any of the phospholipid classes.

10 Thus, the small, unsubstantial increase seen in 22:6n-3 in phosphatidyl choline is consistent with the fact that the relevant diet had added 22:6n-3; however the lack of significant increase in arachidonate in any of the phospholipid classes examined indicates that added arachidonate is not incorporated into these  
15 phospholipid classes, but rather is metabolised or inadequately transported to the brain.

The primary amides, oleamide and arachidonamide, and 18:3 NAE were not detected and are omitted from table 2, which shows the changes in levels of  
20 MAG and NAE expressed as pmols/mg lipid that occurred following feeding of the diets.

Table 2

### Monacyl glycerols (MAG)

Group	C20:4n-6	C22:4n-6	C22:6n-3
Adequate	66.0	3.53	3.87
adequate + SCO	44.4	6.23	5.93
Sow fed	44.1	6.13	6.67

Table 3

*N*-acyl-ethanolamines (NAE)

Group	C16:0	C18:0	C18:1n-9	C18:2n-6
Adequate	114.87	27.90	27.00	8.57
adequate + SCO	149.93	63.87	15.97	2.90
Sow fed	95.07	3.13	1.40	9.80

Table 4

*N*-acyl-ethanolamines (NAE)

Group	C20:4n-6	C20:5n-3	C22:4n-6	C22:5n-3	C22:6n-3
Adequate	6.10	32.87	14.80	3.63	3.80
adequate+ SCO	23.77	172.37	23.07	33.67	36.10
Sow fed	19.97	165.63	29.30	28.00	15.77

5 MAG levels were not statistically significant for 20:4n-6 MAG, 22:4n-6 MAG and 22:6n-3 MAG in animals fed essential fatty acid sufficient diets (*sn*-1 and 2 isomers combined). This is an important finding because specific MAGs, such as 2-AG are known to bind to CB receptors and have bioactivity.

10 In animals fed the 18:2n-6/18:3n-3 sufficient diets, supplementation with AA and DHA led to increases in 20:4n-6 NAE and 22:4n-6 NAE (22:4n-6 is the 2-carbon elongation product of AA), 22:6n-3 NAE, 20:5n-3 NAE and 22:5n-3 NAE (the latter two are retroconversion products of 22:6n-3). The levels of these NAE products were similar to that found in sow milk fed piglets. Thus, it is a  
15 remarkable feature of the invention that when sufficient essential fatty acids are provided in the diet, the supplementation of AA and DHA to levels found in breast milk, has the effect of increasing corresponding NAE products to levels found in sow milk.

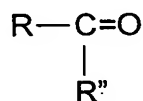
20 The results obtained indicate that supplementation with AA and DHA to formulae having sufficient essential fatty acid had minimal effects on brain phospholipid acyl moieties. However, in striking contrast, the same level of supplementation led to a 4-fold increase in the level of 20:4n-3 NAE present, a 5.2 fold increase in 20:5n-3 NAE, and a 9.5 fold increase in 22:5n-3 and 22:6n-3  
25 NAE.

5 It should be understood that various changes and modifications to the presently preferred embodiments described herein will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the present invention and without diminishing its attendant advantages. It is therefore intended that such changes and modifications be covered by the appended claims.



## Claims

1. A nutritional or therapeutic composition for oral administration which comprises a naturally occurring precursor that is metabolised to a compound having anandamide activity for use as a medicament.
2. A composition according to claim 1 wherein the precursor is a long chain polyunsaturated fatty acid (LCPUFA) or derivative thereof of the general formula X:



Wherein R is the alkenyl moiety of a LCPUFA of total chain length 16-28 carbon atoms with 2-6 double bonds, with the first double bond at the c-1, c-3 c6, c7, c9 c12 position, counting from the non carboxyl (methyl) part of the molecule; and where R'' is selected from -H, lower alkyl, -OH, NH<sub>3</sub>, and NHCH<sub>2</sub>CH<sub>2</sub>OH, or an acid addition salt or complex thereof.

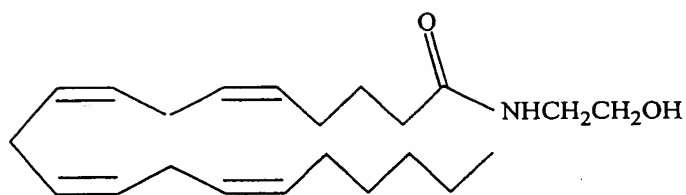
3. A composition according to claim 2 wherein the precursor comprises a molecule having a plurality of formula X.
4. A composition according to claim 2 or 3 wherein the precursor comprises a molecule having from 1 to 3 copies of formula X esterified to a glycerol backbone, in a stereochemical configuration selected from: *sn*-1,2,3; *sn*-1,2; *sn*-1,3; *sn*-2,3; *sn*-1; *sn*-2; *sn*-3.
5. A composition according to any preceding claim wherein the precursor comprises an LCPUFA which is a polyunsaturated fatty acid of 16-28 carbon atoms having from 2 to 6 double bonds, having a methylated-, branched-, cyclic-, conjugated-, non-methylene interrupted-, epoxy-, furanoid-, hydroxyl-, allylic-, trans-, or a seleno- moiety.
6. A composition according to any preceding claim wherein the precursor comprises a fatty acid selected from the group which comprises arachidonate (20:4n-6 AA), linoleate (18:3n-6), gamma linolenate (18:3n-6), dihomogammalinolenate (20:3n-6 DGLA), adrenic acid (22:4n-6), linolenate (18:3n-3), stearidonic (18:4n-3), eicosatetraenoic (20:4n-3), eicosapentaenoate (20:5n-3), docosahexaenoate (22:6n-3DHA), docosapentaenoate (22:5n-3 or 22:5n-6), tetracosapentaenoate (24:5n-3 or 24:5n-6), tetracosahexaenoate (24:6n-3) or the Mead acid (20:3n-9).

7. A composition according to any preceding claim wherein the precursor comprises arachidonate (20:4n-6 AA).
8. A composition according to any preceding claim which comprises an inhibitor of an anandamide-inactivating enzyme (amidase).
9. A composition according to claim 8 wherein the inhibitor is selected from the group which comprises oleate and oleamide, palmitate, palmitoylethanolamide, linoleylethanolamide, 2 palmitoylglycerol, 2-linoleylglycerol.
10. A composition according to claim 8 or 9 wherein the inhibitor is palmitate or palmitoylethanolamide.
11. A composition according to any preceding claim which comprises a triacylglycerol having palmitate and arachidonate attached to its backbone wherein arachidonate is at the *sn*-1 and *sn*-2 positions.
12. A composition according to any preceding claim which comprises a compound which reacts with a CB receptor.
13. A composition according to any preceding claim which comprises a steroidal or non-steroidal anti-inflammatory drug (NSAID).
14. A composition according to any preceding claim which comprises a physiologically acceptable carrier, diluent or adjuvant.
15. A method of production of a nutritional or therapeutic composition for oral administration which comprises the steps of identifying, purifying or synthesising a naturally occurring precursor that is metabolised to a compound having anandamide activity.
16. Use of a composition according to any one of claims 1 to 14 in the manufacture of a nutritional or therapeutic composition for the treatment or prevention of an anandamide-mediated ailment selected from the group which comprises hypertension, glaucoma, insomnia, pain, inflammation, migraine headaches, loss of appetite, nausea, cramps, diarrhoea, gut upsets, intestinal motility disturbances, asthma, nervousness, aggressive behaviour, excessive timidity, inability to sleep, catalepsy, low mood, depression, spasms, poor motor control, tics, excessive stress, spasticity, multiple sclerosis and vocalization, poor language acquisition, skin inflammation and excess nociception.

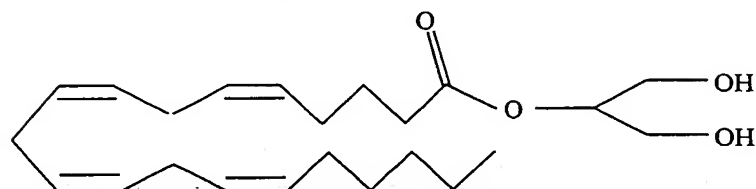
17. A method of treatment of an anandamide-mediated ailment selected from the group which comprises hypertension, glaucoma, insomnia, pain, inflammation, migraine headaches, loss of appetite, nausea, cramps, diarrhoea, gut upsets, intestinal motility disturbances, asthma, nervousness, aggressive behaviour, excessive timidity, inability to sleep, catalepsy, low mood, depression, spasms, poor motor control, tics, excessive stress, spasticity, multiple sclerosis and vocalization, poor language acquisition, skin inflammation and excess nociception which comprises administering an effective amount of a composition according to any one of claims 1 to 14.



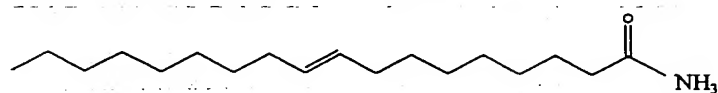
Figure 1



**Anandamide**



**2-AG**



**Oleamide**



Figure 2

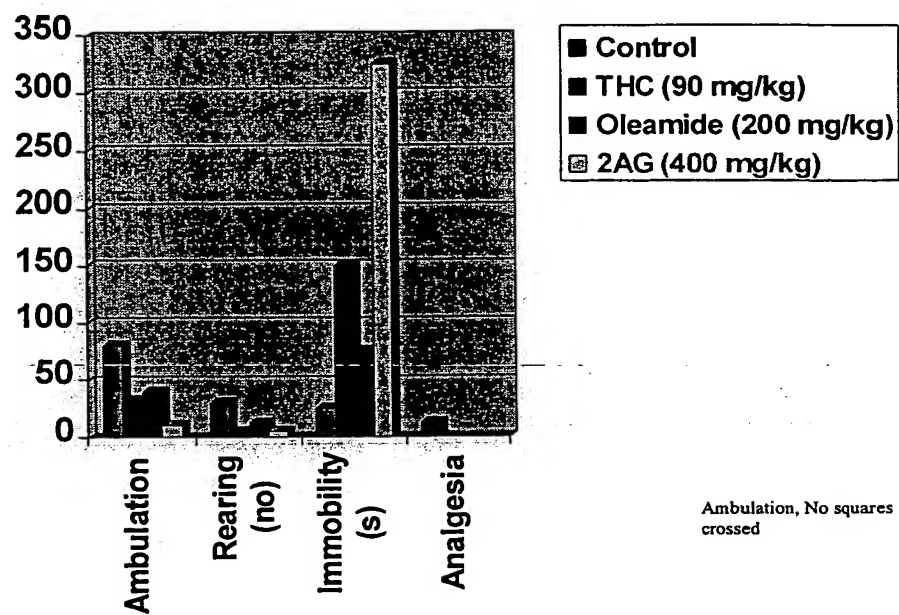






Figure 3

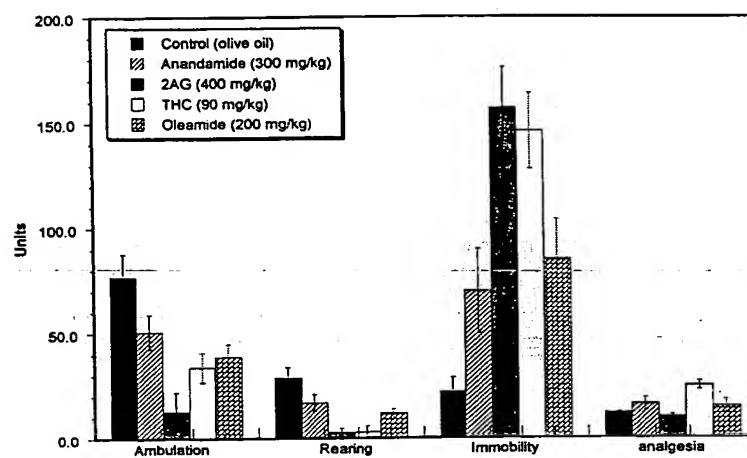




Figure 4

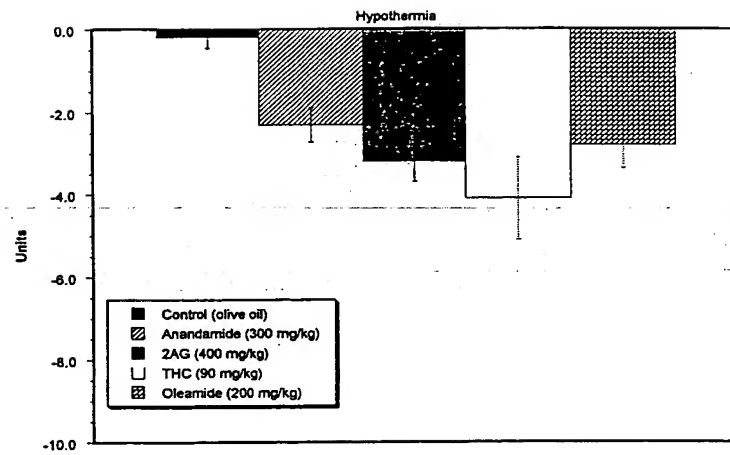




Figure 5

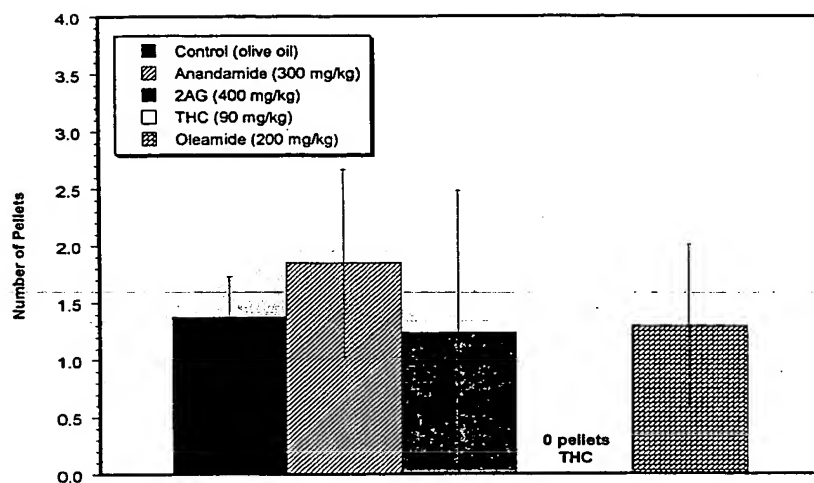




Figure 6

